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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	09/463,958	Confirmation No.: 6995
Applicant	:	Ake Lignell	
Filed	:	01/17/02	
TC/A.U.	:	1654	
Examiner	:	S. D. Coe	
Docket No.	:	LING3003JDB	
Customer No.	:	23364	

RESPONSE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA. 22202-3514

Sir:

This is in response to the Office Action dated March 5, 2004, the period for response to which is set to expire on June 5, 2004.

The examiner has rejected claims 8-25 under 35 U.S.C. § 103(a) as being unpatentable over WO 98/37874 in view of U.S. patent no. 5,229,418. In rejecting the claims the examiner urges that WO '874 teaches a method of treating or preventing inflammation of the gastrointestinal tract caused by *Helicobacter pylori* infection using astaxanthin, including astaxanthin esters and the administration of astaxanthin with carbohydrates and antioxidants. It is also said that WO '874 teaches that the astaxanthin is administered in an amount of 0.01 to 10 mg per kg body weight.

In rejecting the claims the examiner acknowledges that WO '874 does not specifically teach that treating the *H. pylori* infection also treats or prevents indigestion or treats the symptoms of indigestion as set forth in applicant's claims. However, the examiner urges that U.S. '418 teaches that *H. pylori* infections also cause indigestion and thus a person of ordinary skill in the art would reasonably expect that the method of treating or preventing gastritis caused by *H. pylori* infections using astaxanthin taught by WO '874 would also be useful in treating or preventing indigestion associated with *H. pylori* infections. The examiner therefore concludes, based on a reasonable expectation of success, that one skilled in the art would be motivated to use the

astaxanthin taught by WO '874 to treat or prevent indigestion and to treat the symptoms caused by the indigestion itself.

In view of the above, it is clear that the examiner's conclusion regarding obviousness rests upon the examiner's observation that there is a reasonable expectation of success. Applicant submits that the observed reasonable expectation of success is rebutted by the evidence submitted herewith and discussed below. In this regard it is to be noted that evidence showing that there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976).

The examiner's finding of fact concerning the teaching of the cited references is well taken. As correctly noted by the examiner, WO '874 teaches a method of treating or preventing inflammation of the gastrointestinal tract caused by *Helicobater pylori* infection using astaxanthin. On page 3, first paragraph, it is stated that the antioxidative properties of the xanthophylls play an important role in the protection of the hydrophobic lining of the mucous membrane. Further, from table 1 on page 5 of WO '874, one can conclude that the treated animals were not positive for *H. pylori* indicting that the effect of the astaxanthin treatment involves the killing of the bacteria responsible for the inflammation. Thus, the inflammation caused by the bacteria would be cured by taking away the reason for the inflammation, i.e., by killing the bacteria. However, this reference by itself, would not lead one of ordinary skill in the art to conclude that xanthophylls can alleviate symptoms of indigestion in a human. The examiner therefore combines the teaching of WO '874 with U.S. '418.

U.S. '418 states in column 1, lines 33-37 that *H. pylori* infection is associated with histological gastritis, non-ulcer dyspepsia and hypochlorhydria, and may be involved in the pathogenesis of gastric and duodenal ulcer disease. At the bottom of column 1 it is stated that the compounds of U.S. '418 are novel salts of a basic H_2-receptor antagonist furan derivative, and in column 3, lines 31-34 it is stated that these

compounds in addition to possessing the H_2-antagonist antisecretory properties, also have antibacterial activity against *Helicobater pylori*.

Thus, it is clear from the above that the common property of WO '874 and U.S. '418 is the bacteria killing effect.

It will be clear from the following discussion that there would be no reasonable expectation of success, in view of the prior art, that *Helicobater pylori* therapy (i.e., treatment of individuals with a known *Helicobater pylori* bactericide) would lead to effective treatment or prevention of indigestion and the treatment of symptoms caused by the indigestion.

It is clear from the accompanying Curr Treat Options Gastroenterol. that the symptom response to *Helicobater pylori* therapy in patients with functional dyspepsia and a negative endoscopy examination but a positive *H. pylori* test is marginal. (Curr Treat Options Gastroenterol. 2002 Apr; 5(2):153-160). In other words although individuals may be infected with *H. pylori* there is only at best, marginal symptomatic relief achieved by therapy which focuses on the causative bacteria.

Clearly, if there was any reasonable expectation of success, one would expect that successful eradication of *Helicobater pylori* would result in relief of dyspeptic symptoms in patients in which *Helicobater pylori* were eradicated successfully compared to patients in which the *Helicobater pylori* was not eradicated. However, published research clearly indicates that patients, whether eradicated successfully of *Helicobater pylori* or not-eradicated, present a similar six-week and one-year symptom scores. In this regard the examiner's attention is directed to the accompanying abstract from Dig Liver Dis (Dig Liver Dis 2001 Mar; 33(2):125-30). It is also noted in this abstract that *Helicobater pylori* eradication was not the whole management for the relief of dyspeptic symptoms of non-ulcer dyspepsia patients.

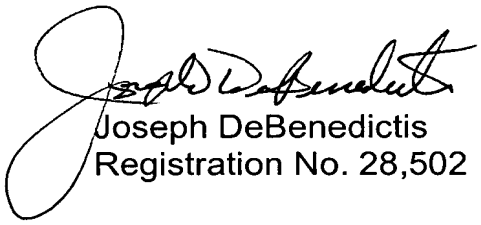
Furthermore, in patients which functional dyspepsia (no lesions detected by endoscopy) review of the literature clearly suggests that the therapeutic benefit of eradicating *Helicobater pylori* is, if it exists, of little value (Gastroenterol Clin Biol. 2003 Mar; 27(3 Pt 2):432-9) (copy of abstract enclosed).

In view of the above, it is clear that killing of *Helicobater pylori* has only a marginal effect on dyspepsia. Moreover, as is evident from the abstract in Curr Treat Options Gastroenterol, the current suggestions for treatment of functional dyspepsia do not include antioxidants like xanthophylls.

In view of the above, it is clear that the prior art references rebut the examiner's conclusion concerning the reasonable likelihood of success and thereby establishes the nonobviousness of the claimed invention. In view of the above arguments, applicant respectfully requests reconsideration and allowance of all the claims which are currently pending in the application.

Respectfully submitted,

Date: June 3, 2004



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Functional (Nonulcer) Dyspepsia.

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Functional (nonulcer) dyspepsia refers to upper abdominal pain or discomfort with or without symptoms of early satiety, nausea, or vomiting with no definable organic cause. The current Rome II criteria help to diagnose functional dyspepsia and avoid misdiagnosis of gastroesophageal reflux disease and irritable bowel syndrome as functional dyspepsia. Assessment of gastric emptying with scintigraphy or breath testing may be useful in identifying delayed gastric emptying in patients with dyspeptic symptoms and may be helpful in patient management. Electrogastrography is a noninvasive test that evaluates for gastric dysrhythmias. Satiety testing is being evaluated as an indirect test for impaired fundic relaxation and visceral hypersensitivity. The symptom response to Helicobacter pylori therapy in patients with functional dyspepsia and a negative endoscopy examination but a positive H. pylori test is marginal. Lifestyle modifications often are suggested for initial treatment of functional dyspepsia. Dietary changes such as frequent small meals, low-fat diet, and avoidance of certain aggravating foods may improve symptoms. Additional measures include cessation of smoking, avoiding excess alcohol intake, and minimizing coffee intake. Antacids and over-the-counter histamine type 2 receptor antagonists may be helpful as an "on-demand" therapy for intermittent symptoms. They are safe and relatively inexpensive. Different subgroups of functional dyspepsia are based on the predominant symptom and may help in choosing an appropriate drug to initiate therapy. If the predominant symptom is epigastric pain (ulcer-like functional dyspepsia), histamine-2 receptor antagonists or proton pump inhibitors are the initial treatment of choice. If fullness, bloating, early satiety or nausea is the predominant complaint (dysmotility-like functional dyspepsia), a prokinetic agent may help. Metoclopramide is the only available effective prokinetic agent at present. If metoclopramide is used, short-term treatment and discussion of possible side effects with the patient are advised. If there is no response to these initial treatments, switching therapy from proton pump inhibitor to prokinetic or vice versa can be tried. If these treatment options fail, patient re-evaluation for other disorders (including other functional bowel disorders) is advised. A low-dose tricyclic antidepressant at bedtime may be helpful for treatment of visceral hypersensitivity.

PMID: 11879596 [PubMed - as supplied by publisher]

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1: Dig Liver Dis. 2001 Mar;33(2):125-30. Related Articles, Links

Ranitidine bismuth citrate or omeprazole-based triple therapy for Helicobacter pylori eradication in Helicobacter pylori-infected non-ulcer dyspepsia.

Chuang CH, Sheu BS, Yang HB, Wu JJ, Lin XZ.

Department of Internal Medicine, National Cheng Kung University, Tainan, Taiwan.

AIM: To test the eradication rate of Helicobacter pylori by ranitidine bismuth citrate-based triple therapy, and evaluate the symptomatic response of Helicobacter pylori eradication therapy for non-ulcer dyspepsia. METHODS: A total of 59 consecutive Helicobacter pylori infected non-ulcer dyspepsia patients were randomly selected to receive either one of two triple therapy regimens, including metronidazole, amoxycillin plus ranitidine bismuth citrate (RAM group) or omeprazole (OAM group). To determine the success of eradication, patients underwent the 13C-urea breath test, 6 weeks and one year after treatment. The dyspeptic symptom scores were also assessed at the time of enrolment, 6 weeks and one year after treatment. RESULTS: Per-protocol and intention-to-treat eradication rates were 77.7% and 70% in RAM group and 83.8% and 68.9% in OAM group (p = non significant). At both the 6th week and at the first year after treatment, the mean symptom scores were lower than pre-treatment scores in the study population, regardless of whether treatment was successful or not. However, patients, whether eradicated successfully or non-eradicated, presented similar 6-week and 1-year scores. CONCLUSIONS: One-week RAM triple therapy, which is cheaper than the OAM regimen, is a relatively effective alternative regimen for Helicobacter pylori eradication in Taiwanese. Triple therapy for Helicobacter pylori eradication was not the whole management for the relief of dyspeptic symptoms of non-ulcer dyspepsia patients.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 11346139 [PubMed - indexed for MEDLINE]

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Related Articles, Links

[Should we take into account Helicobacter pylori infection in a patient with dyspeptic symptoms?]

[Article in French]

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Dyspepsia is a common disorder that presents many clinical dilemmas in patient management despite progress accomplished in the treatment of acid related diseases with proton pomp inhibitors (PPI) and of ulcer disease with eradication of Helicobacter pylori (Hp) infection. Traditionally, uninvestigated patients presenting with dyspeptic symptoms are subjected to prompt endoscopy. This policy is still required in patients older than 45 years or with risk factors of esophageal and gastric cancer. The present review of the literature suggests that in younger patients with no alarming features, a strategy taking into account Hp infection is safe and cost-effective. The best policy consists in an Hp breath test followed by eradication in Hp+ patients. In Hp- patients, empirical treatment with PPI seems the most efficient strategy. In both cases, endoscopy is required when symptoms persist or rapidly recur. In France, where endoscopy is cheap and its accessibly optimal, prompt endoscopy could still be preferable. In absence of well-conducted controlled studies in our country, it is thus not possible to formally recommend the test-and-treat strategy in the management of uninvestigated dyspepsia. In patients with functional dyspepsia (no lesions detected by endoscopy), review of the literature suggests that the therapeutic benefit of eradicating Hp is, if it exists, of little value. Should we eradicate Hp systematically or only in patients mostly concerned by such benefit (ulcer-like and refractory dyspepsia)? The answer will come from the place of eradication of Hp in the general population for prevention of some gastric cancers.

Publication Types:
- Review
- Review, Tutorial

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